

REMARKS

Claims 1-3 and 6-15 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order in which they appear in the prior Office Action.

Because the Advisory Action mailed May 26, 2005 indicated that the Reply After Final filed May 17, 2005 was not entered for purposes of appeal, the claim amendments presented herein are made with respect to the claims as amended on June 29, 2004. Remarks made in the Reply filed May 17, 2005 are incorporated herein by reference to the extent which they remain relevant.

Interview Summary

Applicant Glenn McGall and Applicants' representatives would like to thank the Examiner for granting the in-person interview conducted on July 14, 2005. During the interview, the art and rejections of record were discussed. The Examiner stated that she believed that there was motivation to combine references, as discussed in prior Office Actions. Although Applicants respectfully disagree with the Examiner, this aspect of the rejection was not discussed further. Dr. McGall then discussed the problems solved by the present invention. In particular, Dr. McGall explained the significance of the examples presented in the specification. The Examiner stated that the exemplification in the specification was evidence of unexpected results, and that claims reciting rotations of 90 degrees constituted allowable subject matter. The Examiner requested a Declaration stating that the results in the specification were unexpected. The Examiner indicated that this Declaration would be entered after final.

Claim Amendments

The limitations of Claim 5 have been incorporated into Claim 1. Accordingly, Claims 4 and 5 have been canceled. Claims 6 and 7 have been amended to remove language made redundant in view of the amendments to Claim 1.

No new matter has been added.

Rejection of Claims 1-15 Under 35 U.S.C. 103(a) Over Winkler et al. in View of Goldberg et al.

Claims 1-15 stand rejected as allegedly obvious over US 5,885,837 to Winkler et al. ("Winkler") and US 5,959,098 to Goldberg et al. ("Goldberg"). The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the vertical positioning of Goldberg to the synthesis of Winkler "for the expected benefit of facilitating bubble removal as taught by Goldberg et al." Applicants respectfully traverse the rejection to the extent that it is maintained over the claims as currently amended.

As stated in Paragraph 4 of the Declaration Under 37 C.F.R. § 1.132 of Glenn H. McGall, Ph.D. ("the Declaration"), which is submitted concurrently herewith, the method as presently claimed is unexpected in view of the art of record. Paragraph 3 of the Declaration demonstrates that rotation of a support between attaching or binding steps significantly lowers intra-support variability, as measured by the coefficient of variation and the top to bottom ratio of nucleic acid arrays on the supports. Neither Winkler nor Goldberg, separately or in combination, teach or otherwise suggest that intra-support variability could be reduced by rotation of the substrate between binding or attaching steps. Thus, and as acknowledged by the Examiner, the claimed method produces an unexpected and advantageous result in the nucleic acid arrays obtained therefrom. For at least this reason, the claimed method is not obvious in view of the art of record. Reconsideration and withdrawal of the rejection are respectfully requested.

Applicants respectfully maintain that there is no motivation or suggestion for one of ordinary skill in the art to combine the method of Winkler with the vertical flow cell positioning of Goldberg. Accordingly, Applicants reserve the right to pursue the subject matter removed from the claims in a continuation application.

Rejection of Claims 1-15 Under 35 U.S.C. 103(a) Over Gamble et al. in View of Winkler et al.

Claims 1-15 stand rejected as allegedly obvious over US 5,981,733 to Gamble *et al.* ("Gamble") in view of Winkler. Applicants traverse the rejection to the extent that it is maintained over the claims as currently amended.

As stated in Paragraph 4 of the Declaration Under 37 C.F.R. § 1.132 of Glenn H. McGall, Ph.D. ("the Declaration"), which is submitted concurrently herewith, the method as presently claimed is unexpected in view of the art of record. Paragraph 3 of the Declaration demonstrates

that rotation of a support between attaching or binding steps significantly lowers intra-support variability, as measured by the coefficient of variation and the top to bottom ratio of nucleic acid arrays on the supports. Neither Winkler nor Gamble, separately or in combination, teach or otherwise suggest that intra-support variability could be reduced by rotation of the substrate between binding or attaching steps. Thus, and as acknowledged by the Examiner, the claimed method produces an unexpected and advantageous result in the nucleic acid arrays obtained therefrom. For at least this reason, the claimed method is not obvious in view of the art of record. Reconsideration and withdrawal of the rejection are respectfully requested.

Applicants respectfully maintain that there is no motivation or suggestion for one of ordinary skill in the art to combine the method of Winkler with that of Gamble. Accordingly, Applicants reserve the right to pursue the subject matter removed from the claims in a continuation application.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7633. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

Dated: August 17, 2005

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: _____ Signature: _____

Docket No.: AFMX-P01-017
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
McGall et al.

Application No.: 09/871610

Confirmation No.: 1735

Filed: June 1, 2001

Art Unit: 1634

For: NEW METHODS FOR ARRAY
PREPARATION USING SUBSTRATE
ROTATION

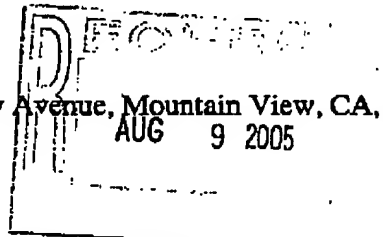
Examiner: B. J. Forman

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132 OF GLENN H. MCGALL, PH.D.

Sir:

I, Glenn H. McGall, Ph.D., of 1121 Sladky Avenue, Mountain View, CA, declare and state that:



1. I am an inventor of U.S. Application No. 09/871,610, filed on behalf of Affymetrix, Inc., 3380 Central Expressway, Santa Clara, California, 95051.
2. I have thoroughly studied the above-identified application and the Office Actions mailed from the Patent Office on February 16, 2005 and May 26, 2005, where claims 1 to 15 are rejected as being unpatentable over Winkler *et al.* (U.S. Patent No. 5,885,837) and Goldberg *et al.* (U.S. Patent No. 5,959,098), and over Gamble *et al.* (U.S. Patent No. 5,981,733) and Winkler *et al.*.
3. From my education, experience and supervision of junior scientists in my laboratory at Affymetrix, I am readily familiar with the level of ordinary skill in the art as

it pertains to the above references and the Examiner's rejection. A copy of my curriculum vitae is attached as Appendix A.

4. Scientists at Affymetrix conducted experiments to determine the effect of substrate rotation, which is reported in the specification of the instant application at page 19, line 20 through page 21, line 8. The example reported in the specification is reproduced below:

In each step, a square wafer is placed in an illumination chamber and light is directed at the wafer through a mask to selectively deprotect and activate specific sites on the wafers. The wafers are then transferred to a synthesis chamber wherein the wafers are held in a vertical position with one corner of the square wafer pointing down. A flowcell is contacted with the wafer and reagents are directed onto the wafer from the bottom to the top. Prior to each step in the synthesis chamber, the wafers are rotated in multiples of 90° (e.g., 90°, 180°, 270°) so that one corner of the wafer is always pointed downward.

This example illustrates the improvement in oligonucleotide array construction and performance that can be achieved using the methods described herein.

Test vehicles, checkerboard of the "213" and "Block 3" sequences were used to perform preliminary experiments. For each of the Checkerboard and Control Block 3 arrays, the oligonucleotides were synthesized in a 23-step process to form arrays of 20-mers. Fluorescein stain, 0.5 hour at 35° C hybridization assay was used to indicate the variation between arrays synthesized. The results were then confirmed by synthesizing Gene expression arrays (e.g., Mu11K), a 74-step process. The standard QC assay, Phycoerythrin/streptavidin (SAPE) stain, 18 hours at 45° C hybridization assay, was used to evaluate the arrays. The average difference of the "Block3" and "Bio C" were analyzed on the Gene Expression probe arrays.

Table 1

Type of Array	Number of wafers	Coefficient of Variation (%)	Top to Bottom Ratio	Rotation type
Checkerboard 213 – control	4	17%, 21%, 19%, 20%	1.4, 1.5, 1.4, 1.4	
Checkerboard 213 – rotated	2	6%, 6%	1.0, 1.0	90 degrees
Checkerboard Block 3 – control	1	8%	1.4	
Checkerboard Block 3 – rotated	1	2%	1.0	90 degrees
Murine gene expression – Block 3 Control	2	55%, 77%	2.9, 5.0	
Murine gene expression – Block 3 Rotated	1	19%	1.2	random 90 degrees
Murine gene expression – Bio C-Control	2	68%, 78%	3.7, 4.9	
Murine gene expression – Bio C – Rotated	1	35%	1.7	random 90 degrees

As can be seen from the table of data above, rotating the wafers during synthesis led to a significant reduction in intra wafer variability of from about 50% (68% CV versus 35% CV) to about 75% (8% CV versus 2% CV).

Figure 2 is a graph that illustrates the average difference in control versus rotated arrays. In this experiment, lot 95296 as a control exhibited Block 3 average

differences of about 50-150. The rotated lots, 95297 and 95299, exhibited average differences of about 45-85 and about 40-70, respectively, indicating the reduced variability for rotated lots.

Figure 3 provides an analysis of chips from different portions of each wafer. In this graph, b = bottom, c = center, t = top, l = left and r = right. As can be seen in Figure 3, the control wafer (296) exhibited markedly wider ranges of average difference, while the rotated wafers (297 and 299) provided more consistent results between the portions of the wafer.

- The results obtained in the example reproduced in Paragraph 3 are unexpected in view of the art of record. Based upon this art, one of ordinary skill in the art would not

have expected that rotation of a support upon which a nucleic acid array is synthesized prior to, coincident with or subsequent to at least one attaching or binding step in the synthesis would result in a reduction in intra-support variability in the nucleic acid arrays. In particular, one of ordinary skill would not have predicted the significant decrease in intra-support variability when the support was rotated 90 degrees between attaching or binding steps.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code and that willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Dated: 08-05-05

Signature: Glenn H. McGall

Glenn H. McGall, Ph.D.